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AN OVERVIEW OF IMPLANTABLE DRUG DELIVERY SYSTEMS

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ABSTRACT:

Traditional drug delivery systems lack precise control over drug release patterns and the absorption of drug concentrations at the target site. An inherent issue with traditional dosage forms is the indistinct concentration of the drug in plasma. In response to these challenges, researchers and pharmaceutical scientists have dedicated their efforts to enhancing drug delivery systems, leading to the emergence of Novel Drug Delivery Systems (NDDS). NDDS employs innovative approaches and technologies to achieve controlled drug release at low concentrations, often following a zero-order release pattern. A significant advancement within NDDS is the development of Implantable Drug Delivery Systems (IDDS). IDDS represents a novel approach to drug delivery, ensuring controlled release at the specific implantation site. This study delves into the mechanism of drug release from implantable therapeutic systems, preparation evaluation parameters, and prospects of the implantable drug delivery system (IDDS).

KEYWORDS: Implants, Polymers in implants, Methods, mechanism, Evaluation of Implant.

I. INTRODUCTION:

In 1861, Lafarge pioneered the concept of implantable systems for administering sustained-release drugs. The initial application involved the creation of solid implants containing steroid hormones, enabling long-term drug delivery. Implantable drug delivery systems, abbreviated as IDDS, are specifically designed to be positioned beneath the skin, releasing drugs into the bloodstream without the need for repetitive needle insertions.

Thus, an IDDS is characterized as a sterile drug delivery device intended for subcutaneous implantation. It possesses the capability to dispense drugs at a controlled rate over an extended period, featuring a rod-shaped polymeric inner matrix with an elongated body and two ends.

The predominant method for drug administration, accounting for approximately 90% of cases, is oral delivery. However, this approach presents challenges, including unpredictable plasma concentration, degradation in the acidic environment of the stomach, irritation of the gastrointestinal tract, and the occurrence of first-order and first-pass metabolism, leading to reduced drug concentrations in the bloodstream. Overcoming these drawbacks is crucial, especially when certain drugs cannot be administered orally due to degradation at extreme pH levels or susceptibility to gastric juices and enzymes. Global research and experiments are underway to identify optimal drug delivery systems that ensure controlled and sustained release both in the bloodstream and at the target site of action. The development of novel drug delivery systems, both nationally and internationally, aims to address the limitations of traditional methods, providing a safe and efficacious means of drug delivery. These innovative systems are designed to deliver drugs precisely to targeted organs or sites where localization of action is essential.

The concept of implantable drug delivery systems gained prominence in 1938 when scientists Deans by and Parkes introduced a compressed pellet through subcutaneous administration. An implantable drug delivery system involves surgically inserting the implant into the body, representing a medical achievement that aims to enhance the effectiveness of medications while reducing the risk of life-threatening conditions such as tumors, ischemic heart attacks, strokes, and HIV/AIDS. This system proves particularly beneficial for medications with low bioavailability through the digestive tract, including antibiotics, NSAIDs, contraceptives, and more. The widespread need for such a robust drug delivery system is evident, as it caters to a significant population of individuals and animals. While various delivery systems have been developed, not all have found common medical applications, despite their potential in providing prolonged and sufficient drug dosing to patients.

Implantable devices have ability to minimise the need of frequent drug intake as well as authorize medication needs with approachable way. At present, these devices are commonly employed in many therapeutic areas such as contraception, chemotherapy, dentistry etc. The expanding production and market availableness of implants are evident of immense growth in this sector (figure 1).

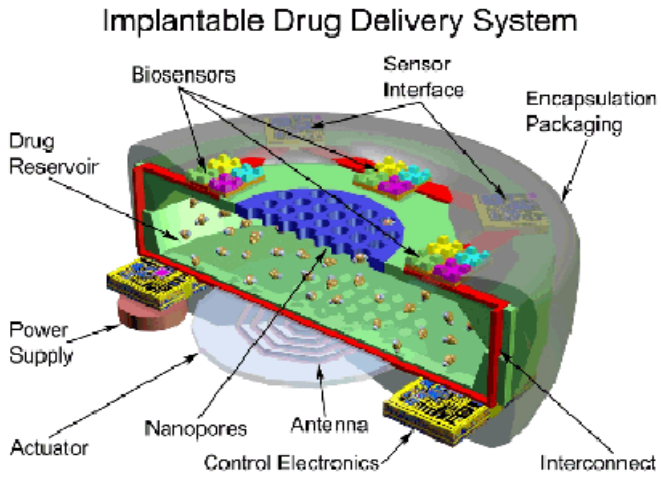

Figure 1: Illustration of an implantable drug device

Implantables are commonly selected for their property of extended use with constant release of medicament which will eventually promote the patient compliance.

- **Ideal Properties of an Implantable Drug Delivery System:**

1. The material must exhibit environmental stability.
2. It must demonstrate biocompatibility.
3. Ease of manufacturing and sterilization are essential criteria.
4. The material should facilitate controlled drug release rates.
5. Enhancing patient compliance by minimizing drug dosing frequency over the treatment duration is a crucial factor.
6. Affordability is an important consideration.
7. Mechanical strength is a key attribute.
8. It should eliminate the need for surgical procedures.

- **Advantages of the Implantable Drug Delivery System:**

1. **Convenience:** Effective concentration of drug in the blood can be maintained for longer period of time by techniques such as continuous intravenous infusion or repeated injections. On the other hand, under these treatments patients are regularly required to visit hospital throughout administration for uninterrupted medical monitoring. A short-acting medicine worsens the condition, as the quantity of injections or the infusion rate need to be increased to maintain a therapeutically effective level of the drug. On the other hand, implantation treatment permits patients to get medication outside the hospital setting with marginal medical observation.
2. **Compliance:** By allowing a reduction, or complete elimination, of patient-involved dosing compliance is increased hugely. Patient can forget to take a medicine, but drug delivery from an implant is not dependent of patient input. Periodical refilling is involved in some implantables but despite this limitation the patient has less involvement in delivering the required medication.

3. **Potential for controlled release:** Implants are available which deliver drugs by zero order controlled release kinetics.

   The advantages of zero order controlled release are: (a) Peaks (toxicity) and troughs (ineffectiveness) of conventional therapy is avoided, (b) Dosing frequency is reduced,

   (c)Patient compliance is increased.
4. **Potential for bio-responsive release:** Bio-responsive release from implantables is an area of on-going research.
5. **Potential for intermittent release**: Intermittent release can be facilitated by externally programmable pumps. Intermittent release can facilitate drug release in response to such factors as:

   (a) Circadian rhythms,

   (b) Fluctuating metabolic requirements,

   (c) Pulsatile release of many peptides and proteins.
6. **Flexibility:** In the choice of materials, methods of manufacture, degree of drug loading, drug release rate etc. considerable flexibility is possible. From a regulatory viewpoint, it is regarded as a new product and can lengthen the market protection of the drug for an additional 5 years (for a new drug entry) or 3 years (for existing drugs).

- **Disadvantages of the Implantable Drug Delivery System:**

1. **Invasive:** For inserting implants, the patients have to undergo a major or a minor surgical process.
2. **Termination:** Non-biodegradable polymeric implants need to be surgically removed from the body at the end of the treatment.
3. **Danger of Device Failure:** If the device fails to operate properly during the treatment due to any reason, the device should be surgically removed from the patient's body.
4. **Limited to Potent Drug:** Only potent drugs (effective even in very small amount) can be used since the device is of very small size to reduce patient's discomfort.
5. **Adverse Reaction:** Since a high concentration of drug is delivered to the implantation site via device, a chance of adverse reaction due to this local high concentration always exists.

II. MECHANISM OF DRUG RELEASE FROM IMPLANTABLE THERAPEUTIC SYSTEM:

Numerous strategies have been developed over several years to achieve controlled release drug delivery for extended durations through the use of implantable drug delivery systems. Presently, these approaches can be categorized as follows:

A. Controlled Drug Delivery through Polymer Membrane Permeation:

i) This type of controlled drug delivery device involves enclosing a drug reservoir within a capsule-shaped or spherical compartment.

ii) A rate-controlling polymeric membrane is applied to cover this system.

iii) The drug reservoir may consist of solid particles or solid particles dispersed in a liquid or solid dispersing medium.

iv) The encapsulation of the drug reservoir within the polymeric membrane is achieved through methods such as encapsulation, microencapsulation, moulding, extrusion, etc.

v) An example of this approach is the Norplant sub-dermal implant.

B. Polymer Matrix Diffusion-Controlled Drug Delivery System:

i) This type of controlled drug delivery system involves creating a reservoir by dispersing solid particles in a lipophilic or hydrophilic polymer matrix.

ii) The dispersion can be achieved by mixing the solid drug dosage form with a liquid or semi-solid polymer matrix at room temperature, followed by cross-linking of polymer chains.

iii) The resulting drug-polymer dispersions are then shaped into various drug delivery devices through molding or extrusion.

iv) An alternative method involves dissolving the drug solid or the polymer in an organic solvent, followed by conservation or solid evaporation at an elevated temperature under vacuum to form microspheres.

v) An example of this type of system is the Compudose implant.

C. Hybrid Membrane-Matrix Drug Delivery System:

i) This system combines features of both polymer membrane permeation and polymer matrix permeation controlled drug delivery systems.

ii) Similar to the polymer membrane permeation controlled system, this hybrid device maintains constant drug release kinetics, minimizing the risk of dose dumping from the reservoir compartment.

iii) Similar to the matrix diffusion system, the drug reservoir of this hybrid device involves a homogeneous dispersion of solid drug particles within a polymer matrix.

iv) Notably, the entire reservoir is enclosed within a rate-controlling polymeric membrane.

v) Consequently, the membrane-matrix hybrid drug delivery system can be classified as a sandwich-type implantable device.

vi) An illustrative example of this technology is the Norplant II sub-dermal implant.

D. Microreservoir Partition Controlled Drug Delivery System:

i) This type of controlled-release drug delivery device features a drug reservoir consisting of a suspension of drug crystals in an aqueous solution of water-miscible polymer, forming a homogeneous dispersion.

ii) High energy dispersion techniques are employed to achieve microdispersion.

iii) Drug delivery devices of various sizes and shapes can be obtained through extrusion and molding methods.

iv) Depending on the physicochemical properties of the drug, a biocompatible polymer layer can be applied to the device to modify the mechanism and rate of drug release.

v) An illustrative example is the Syncromate implant.

E. Osmotic Pressure-Activated Drug Delivery System:

i) This controlled release drug delivery device utilizes osmotic pressure as the primary energy source for activating and regulating drug delivery at the implantation site.

ii) The drug reservoir in this system can be either a solution or in a semi-solid state, enclosed within a semi-permeable compartment with controlled water permeability.

iii) An example of such a system is the Alzet osmotic pump.

F. Vapour Pressure-Activated Drug Delivery System:

i) The primary energy source for this controlled release drug delivery device is vapour pressure, which activates controlled drug delivery.

ii) In this system, the drug reservoir consists of a solution contained within an infusate chamber.

iii) The infusate chamber is separated from the vapour pressure chamber by freely movable bellows.

iv) The vapour pressure chamber contains a vaporizable fluid, such as fluorocarbon, which vaporizes at body temperature, generating vapour pressure that propels the bellows in an upward direction.

G. Magnetically-Activated Drug Delivery System:

i) This controlled release drug delivery device relies on electromagnetic energy as its primary source to activate controlled drug delivery and regulate the release rate.

ii) The device incorporates a magnetic wave triggering mechanism.

iii) A sub-dermally implantable, magnetically-modulated hemispherical drug delivery device was created by placing a small donut-shaped magnet at the center of a polymer matrix.

iv) The matrix contains a uniform dispersion of a drug with low polymer permeability at a relatively high drug-polymer ratio, forming a hemispherical pellet.

v) The outer surface of the hemispherical pellet is coated with a pure polymer, such as ethylene vinyl acetate copolymer.

vi) Applying an external magnetic field activates the drugs through electromagnetic energy, leading to a significantly higher rate of release from the pellet.

vii) As an illustration, Bovine Serum Albumin (BSA) can be administered using this innovative device.

III. CONCEPT OF IMPLANTS:

An implant refers to a medical device utilized to replace a missing biological structure, offering support to a damaged biological structure or enhancing the functionality of an existing one. Unlike transplants involving biomedical tissue, medical implants are artificially created devices. The surface of these implants that comes in contact with the body is composed of a biomedical material, such as titanium, silicone, or apatite, chosen for its functional effectiveness. Occasionally, implants may incorporate electronics, as seen in artificial pacemakers and cochlear implants. Some implants, including subcutaneous drug delivery devices in the form of implantable pills or drug-eluting stents, exhibit bioactive properties.

1) Non-Degradable Systems:

Several types of non-degradable implantable drug delivery systems are available in the market, of which the non-degradable matrix systems and reservoir systems are the most common forms (**Figure 2**).

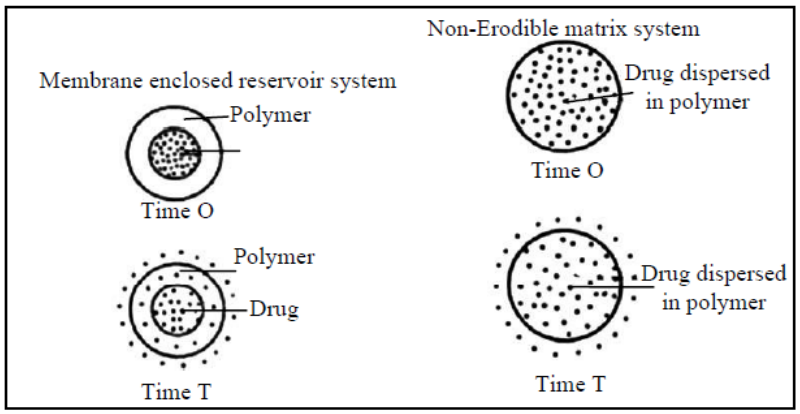

Figure 2: Cross-Sectional View of Non-Erodible Reservoir and Matrix Systems, Showing Diffusion of the Drug across the Polymer

In the polymeric matrix system, the drug is evenly distributed throughout the matrix material. This polymeric matrix facilitates slow drug diffusion, ensuring sustained release from the delivery system. In the reservoir-type system, a dense drug core is encased by a permeable non-degradable membrane, controlling drug diffusion into the body based on the membrane's thickness and permeability. The release kinetics of the drug from this system indicate that a constant equilibrium between the drug concentration in the reservoir and the inner surface of the membrane results in zero-order release kinetics. However, this system has drawbacks:

- The non-degradable outer membrane requires a minor surgical procedure for removal after drug release.
- Membrane rupture may lead to drug dumping, causing toxic side effects due to drug plasma concentrations exceeding safety levels. Consequently, the reservoir system has become less favored for drug delivery due to the risk of drug dumping.

Matrix systems are also utilized as non-degradable implants, comprising uniformly distributed drugs in a solid non-biodegradable polymer. Similar to reservoir systems, matrix systems facilitate drug particle diffusion through the non-degradable fibrous network, providing sustained drug release. However, the release kinetics are not constant and depend on the agent's volume fraction in the matrix; a higher concentration results in greater release. Another non-degradable system is the magnetically controlled release system, where small magnetic beads are evenly dispersed in a polymer (Figure 3). When exposed to a biological system, the drug undergoes normal diffusion due to a concentration gradient. However, exposure to an external oscillating magnetic field leads to a rapid release of larger drug quantities. This type of drug delivery system offers the significant advantage of controlling drug release kinetics using external magnetic stimuli.

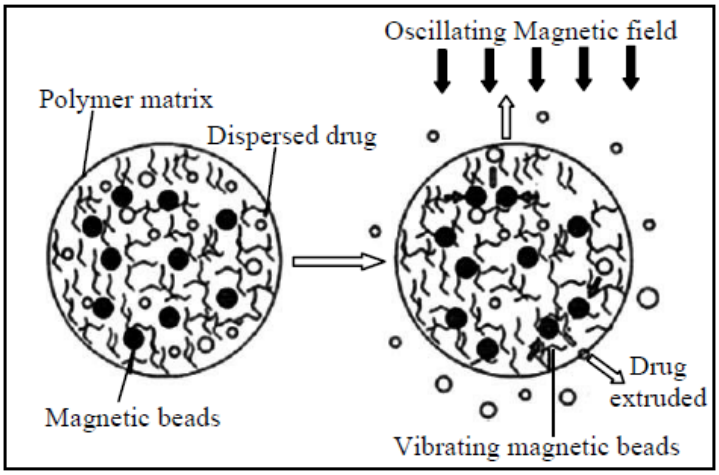

Figure 3: Schematic of a Magnetically Controlled Polymeric Drug Delivery System Illustrating Increased Drug Release from the System after Exposure to an Oscillating Magnetic Field

2) Biodegradable Systems:

Biodegradable delivery systems are widely preferred over non-degradable ones due to their use of inert polymers that are absorbed or excreted by the body, eliminating the need for surgical removal after treatment. However, developing biodegradable systems is more complex, requiring consideration of various factors such as polymer degradation kinetics, affected by body pH, temperature changes, and surface area alterations. To maintain a constant drug release, the shape of the delivery system should be carefully designed. Some manufacturers address the issue of changing surface area by using bioerodible inert cores coated with the active drug matrix.

Another challenge is the slower drug diffusion compared to bioerosion, influenced by the chemical nature of the polymer. Two main types of biodegradable delivery systems are reservoir systems, similar to non-degradable ones, and monolithic systems, where the drug dispersed in a polymer slowly erodes.

Popular polymers in research include polyglycolic acid, polylactic acid, polyglycolic-lactic acid, polyaspartic acid, and polycaprolactone. Ethyl vinyl acetate copolymer matrices have also been studied for macromolecular drug delivery, such as insulin.

IV. METHODS OF PREPARATION OF IMPLANTS:

There are mainly three methods for the preparation of implants that are discussed below:

A. Extrusion method:

Firstly selected drug is dissolved in a suitable solvent system to produce a solution. After that polymer is added into the solution slowly and allowed to stand for 10-15 minutes for soaking purposes. The swollen material developed had been blended uniformly till it forms a dough-like material. The dough was transferred into the extruder cylinder and had been extruded in the form of long rods by the help nozzle. Implants dried the whole night at room temperature, and then cut into the optimum size and dried at 40^{o}C.

B. Compression Method:

The polymer and drug were dissolved to develop the solution. The produced solution was subjected to freeze-drying to produce a uniform cake. The cake was subjected to compression for the development of the implant.

Implants have been developed by utilizing a Carver hydraulic press at a pressure of 1 metric ton, utilizing a stainless steel system developed for this objective, comprised of a 1mm diameter cylindrical punches set.

C. Molding Method:

Solution of polymer and the drug was firstly prepared in a suitable solvent system and then subjected for the lyophilization and converted to a uniform cake after that before the prepared cake was molded into rods through a Teflon sheet heated on a hot plate at a temperature about 100-120^{o} C.

V. ASSESSMENT CRITERIA FOR IMPLANT EVALUATION:

Following the preparation using an appropriate method, an implant undergoes scrutiny based on several parameters including shape and size, uniformity of thickness, weight variation, and stability studies.

a. Size and Shape:

The assessment of implants involves the use of Vernier Calipers under light conditions to determine their size accurately.

b. Uniformity of Thickness:

Implants are individually examined using Vernier Calipers to ascertain precise thickness readings, highlighting any variations among different implants. The mean value is obtained by evaluating at least three samples.

c. Uniformity of Weight:

Also referred to as the weight variation test, this examination aims to establish the consistency in the weight of each implant. Twenty implants are randomly selected, and the mean weight is calculated. No more than two implants should exceed the mean weight, and none should weigh double the average.

d. % Swelling Index:

To determine the swelling index, prepared implants are immersed in a swelling medium with neutral pH at room temperature for an hour. Post-immersion, the implant is weighed, and any excess solution is removed using a dry filter paper. The % swelling index is calculated using the following formula:

$$\text{Swelling Index} = \frac{W2 - W1}{W1} \times 100$$

W2 and W1 are the weight of the implant after 1 hour and in the dry state respectively.

e. *In-vitro* dissolution studies:

In-vitro dissolution studies are important to determine the drug release and the stability of drug products**.** *In-vitro* dissolution study is carried out with the help of the rotating paddle, the method comes under the category of apparatus 2. The dissolution medium was filled in the vessel and the optimum temperature and rpm were set, after put the implant in the vessel and start rotating the paddle and then take the sample after time intervals of the predetermined time. And the collected samples were examined under a UV visible spectrophotometer at a specified wavelength. The dissolution study performs a minimum of three times, and the average observation was taken.

f. Stability studies:

The purpose of stability testing (the International Conference on Harmonization [ICH], 2004) is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, enabling recommended storage conditions, retest periods, and shelf lives.

Table 1: ICH guidelines for stability studies

Case	Study type	Storage condition	Duration
General	Long term	25ºC±2ºC/60%±5% or 30ºC±2ºC/65%±5%	12 months
	Intermediate	30ºC±2ºC/65%±5%	6 months
	Accelerated	40ºC±2ºC/75%±5%	6 months
Stored in refrigerator	Long term	5ºC±3ºC	12 months
	Intermediate	25ºC±2ºC/60%±5%	6 months
Stored in freeze	Long term	-20ºC±5ºC	12 months

g. Drug and polymer interaction study: Infrared spectroscopy of API/drug and polymers was done by the FTIR. After the preparation implant was also subjected to FTIR analysis to check the compatibility of the drug with additives.

VI. APPLICATIONS:

Implantable Drug Delivery Systems (IDDS) find diverse applications in the field of healthcare.

a. Ocular Disease: Various implantable systems have been explored for prolonged ocular drug delivery. An example is Ocusert, a membrane-controlled system containing pilocarpine base and alginic acid in a drug reservoir surrounded by an ethylene-vinyl acetate membrane.

b. Contraception: The FDA recently approved Norplant, a sub-dermal implant designed for long-term delivery of the contraceptive agent levonorgestrel. It comprises six silicone membrane capsules, each containing 36mg of levonorgestrel, placed sub-dermally on the upper arm or forearm.

c. Dental Application: Polymeric implants have been researched for dental applications, specifically for the local and prolonged administration of fluoride, antibacterials, and antibiotics. Various formulations, including hydroxyethyl methacrylate and methyl methacrylate copolymer hydrogel, have been studied for rate-controlled drug release.

d. Immunisation: Polymeric implants are under investigation for enhancing immune responses to antigens, allowing pulsatile or continuous administration over an extended period. The immunisation efficacy of ethylene-vinyl acetate copolymer pellets containing model antigen bovine serum albumin has been explored.

e. Cancer: Silicone rod implants (similar to those used for delivering levonorgestrone) have been tested for delivery of testosterone propionate or ethinyl estradiol in prostate cancer patients. Lupron depot is an implantation system used for providing one month depot release of leuprolide acetate [a synthetic analogue of Gonadotropin-Releasing Hormone (GnRH)].

f. Narcotic Antagonists: Naltrexone has been evaluated in implant from long-term delivery of narcotic antagonists. Naltrexone freebase, its hydrochloride or the pamoate acid salt has been prepared in various polymers and dosage forms for prolonged narcotic antagonist activity. Though *in vitro* delivery of up to 50 days has been achieved by some of the systems, *in vivo* duration of release was found to be shorter.

Polylactide, polylactic glycolide and polycaprolactone-co-lactide polymers were evaluated in biodegradable polymer-coated microspheres, containing naltrexone base. Diffusion-controlled, linear naltrexone release was observed from the coated microspheres for about 50 days. These microspheres produced morphine antagonist response in implanted rats for 60 days.

VII. CONCLUSION:

Drug administration encompasses diverse routes, such as oral delivery, transdermal application, and implantation. Implants play a crucial role in drug delivery systems, offering efficient and sustained release over an extended period. Notably, implantable drug delivery systems exhibit controlled or zero-order release, making them suitable for targeted applications like contraceptive implants. These implants, inserted into the uterus through a minor surgical procedure, gradually release drugs, providing contraception for up to a decade. The advancements in implantable drug delivery systems include features such as zero-order release, reduced toxicity, targeted drug delivery, lower drug quantities, and improved patient compliance. Additionally, these innovations can potentially lead to fewer hospitalizations, opening new avenues in healthcare. The study delves into the mechanisms of drug release from implants, highlighting four distinct methods. It lays the groundwork for future research on implantable drug delivery systems and aids in the selection of appropriate polymers, with a focus on biodegradable and non-biodegradable types. Non-biodegradable polymers, commonly used in diffusion-controlled implantable systems, are explored in detail. The study encompasses approaches to implantable drug delivery system development, formulation and preparation of implants, and evaluation parameters.

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